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Re: Application No. 08/919,501

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Transmittal (2 pgs.)
Reply Brief (11 pgs.)
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Attorney Docket No.: SALK2190
(088802-5001)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: O'Gorman and Wahl

Title: SITE-SPECIFIC RECOMBINATION IN EUKARYOTES AND CONSTRUCTS USEFUL THEREFOR

Appl. No.: 08/919,501

Filing Date: August 28, 1997

Examiner: M. Wilson

Art Unit: 1633

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August 5, 2002
(Date of Deposit)

TRANSMITTAL

Commissioner for Patents
Washington, D.C. 20231
BOX AF

Sir:

Transmitted herewith for the above-identified application please find:

1. Reply Brief
2. Request for Oral Hearing (in dupl.)

Respectfully submitted,

Date: August 5, 2002

By

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(088802-5001)

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REQUEST FOR ORAL HEARING

Commissioner for Patents
Washington, D.C. 20231
BOX AF

Sir:

Pursuant to 37 C.F.R. 1.194(b), Applicants respectfully request an oral hearing before the Board. This request is accompanied by the requisite fee of $140.00 as set forth in 37 C.F.R. 1.17(d) to be charged to Deposit Account No. 50-0872. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 50-0872.

Respectfully submitted,

Date: August 5, 2002

By _____

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DUPLICATE

Atty. Dkt. No.SALK2190
(088802-5001)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: O'Gorman and Wahl

Title: SITE-SPECIFIC RECOMBINATION IN EUKARYOTES AND CONSTRUCTS USEFUL THEREFOR

Appl. No.: 08/919,501

Filing Date: August 28, 1997

Examiner: M. Wilson

Art Unit: 1633

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Respectfully submitted,

Date: August 5, 2002

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PATENT
Attorney Docket No.: SALK2190
(088802-5001)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: O'Gorman and Wahl	Group Art Unit: 1633
Application No.: 08/919,501	Examiner: M. Wilson
Filing Date: August 28, 1997	CERTIFICATE OF FACSIMILE TRANSMISSION I hereby certify that this paper is being facsimile transmitted to the United States Patent and Trademark Office, Washington, D.C., on the date below.
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Box AF
Commissioner for Patents
Washington, D.C. 20231

REPLY BRIEF

Sir:

Applicant (herein, "Appellant") submits this Reply Brief in response to the Examiner's Answer (Paper No. 30, mailed June 5, 2002) in accordance with 37 C.F.R. § 1.193(b)(1). No fee is believed due in connection with this submission. If this is incorrect or if any additional fees are due in this regard, please charge or credit Deposit Account No. 50-0872 for the appropriate amount.

In re Application of: O'Gorman and Wahl
Application No.: 08/919,501
Filing Date: August 28, 1997

PATENT
Attorney Docket No.: SALK2190
(088802-5001)

Table of Contents

In re Application of: O'Gorman and Wahl
Application No.: 08/919,501
Filing Date: August 28, 1997

PATENT
Attorney Docket No.: SALK2190
(088802-5001)

I. Introduction

The Examiner's Answer (Paper No. 30) asserts several unsupported or erroneous statements in response to Appellant's Reply Brief. In particular, Appellant respectfully disagrees with certain assertions made by the Examiner regarding the Summary of the Invention, the Grouping of Claims, and the rejections of the claims, both under 35 U.S.C. §112, first paragraph and 35 U.S.C. § 112 second paragraph, as discussed in further detail below.

II. Summary of the Invention

Appellant respectfully submits that Appellant's Summary of the Invention as presented in the Appeal Brief accurately reflects the invention, and the Examiner's attempts to restrict the use of ES cells containing recombinase to excise DNA encoding a marker protein are inappropriate.

Appellant respectfully disagrees with the Examiner's assertion that the Summary of Invention contained in the Appeal Brief is deficient (see Examiner's Answer, Paper No. 30, at page 2, line 14). Specifically, the Examiner merely recites his own view of the invention, rather than pointing out why Appellant's Summary of the Invention is deficient (see Examiner's Answer, Paper No. 30, at page 2-3). The present invention is based on the discovery that recombinase-encoding nucleic acid constructs can be incorporated into the genome of embryonic stem (ES) cells to be later activated and expressed during the development of the resulting transgenic organisms. These constructs are expressed at high levels in the germline of transgenic organisms by means of germline-specific promoters to produce active recombinase.

The Examiner improperly and repeatedly refers to the use of invention ES cells in combination with DNA encoding a marker protein flanked by recombination sites (see Examiner's Answer, Paper No. 30, at page 2-3). However, in contrast to the Examiner's narrow interpretation of the invention, the claimed recombinase construct can be used in combination with any target gene of interest flanked by recombinase recombination sites (see Appeal Brief, Summary of the Invention, at pages 6-7; and specification, for example, at page 4, lines 7-17).

Therefore, the Examiner's view of the invention is unduly narrow, and is not reflective of the invention as contemplated in the specification as filed. Accordingly, it is respectfully submitted that Appellant's Summary of the Invention is not deficient in any respect.

III. Grouping of Claims

Appellant respectfully submits that each group as identified by the Appellant is separately patentable for the reasons presented in the Appeal Brief (see Appeal Brief, at pages 9-11). Although the Examiner has provided multiple alternative groupings of the claims (see Examiner's Answer, Paper No. 30, at pages 3-7), the Examiner has failed to provide an explanation as to why the claims as grouped in the Appeal Brief are not separately patentable.

Contrary to the Examiner's proposed Grouping of the Claims, Appellant has grouped the claims according to whether the claims are directed to patentably distinct ES cells or patentably distinct methods using invention ES cells, *i.e.*, based on the subject matter of the claims (see Appeal Brief, at pages 9-11). Thus, claims 12-15, 18-24 and 26 stand or fall together, being directed to non-human ES cells comprising the recombinase construct as claimed. Claims 49-51 are also directed to ES cells comprising the recombinase construct as claimed, but each of these claims stands or falls alone based on the different type of non-mammalian source for the ES cells.

With respect to the types of methods claimed, claims 28-31 stand or fall together; claims 32 and 34 stand or fall together; claims 35-39 stand or fall together; claims 40-42 stand or fall together; claim 43 stands or falls alone; claim 44 stands or falls alone; claim 46 stands or falls alone; claim 47 stands or falls alone; claim 48 stands or falls alone; based on the different steps of the methods claimed, and /or the different animal being claimed.

IV. Argument

1. 35 U.S.C. § 112, first paragraph Rejection of Claims 12-15, 18-24, 26, 28-32, 34-44 and 46-51

The Examiner improperly characterizes the invention in order to use a reference as evidence of non-enablement.

In response to Appellant's Appeal Brief, the Examiner improperly broadly asserts that "germline transmission is essential to the invention" (see Examiner's Response, Paper No. 30 at page 13, line 21), without considering each of the claims independently in applying the Mullins reference of record as alleged evidence of non-enablement. Appellant respectfully submits that there is in fact clearly no requirement for "germline transmission" in claims of the present invention. Thus, the fact that Mullins may state that ES cells providing germline transmission were only available in mice is completely irrelevant to the present claims.

As argued in the Appeal Brief, Mullins clearly states that ES cells are obtainable from a variety of species. The *Examiner acknowledges* this teaching of Mullins (see Examiner's Answer, Paper No. 30, page 13-14 bridging sentence). Claims 12-15, 18-24, 26 and 49-51 are directed to ES cells, wherein the ES cells have been modified (*e.g.*, transfected) to contain a nucleic acid construct comprising a recombinase. Methods of producing ES cells containing additional nucleic acid constructs were clearly known to one of skill in the art at the time of filing, and examples are also provided in the specification, *e.g.*, page 9, lines 7-23. This is all that is required by claims 12-15, 18-24, 26 and 49-51. There is clearly no requirement for "germline transmission" in any of these claims.

Similarly, there is no requirement for "germline transmission" in any of claims 28-32 and 34, which are generally directed to excision of a target marker in ES cells also expressing recombinase. Briefly, these claims require introducing two constructs into ES cells, and developing the ES cells through gametogenesis, at which time-point the recombinase becomes expressed. Thus, the claims require only germline expression of recombinase in the resulting

chimeric animal, and, as noted with the previous claims, there is no requirement for "germline transmission" to future generations. The fact that Mullins may state that ES cells providing germline transmission were only available in mice is also irrelevant to these claims, because Mullins is silent on germline expression upon development of ES cells.

Furthermore, there is no requirement for "germline transmission" in any of claims 44-48, which are generally directed to the generation of recombinase recombinant animals. Briefly, these claims require combining a recombinase construct with ES cells, and developing the ES cells to term to allow expression of the recombinase, and as noted with the precious claims, there is no requirement for "germline transmission" to future generations.

Therefore, the specification as filed clearly enables non-human mammalian ES cells and methods of use thereof as claimed.

The Examiner continues to unreasonably argue against the art-accepted definition of germline-specific promoters.

In spite of Appellant having provided evidence in the form of publications that Appellant's usage of the term "germline specific promoter" was consistent with its use in the field, especially in the context of transgenic mice (enclosed with Appeal Brief as Appendix B), the Examiner persists with the unsupported position that the exemplary germline-specific MP1 promoter used in the working examples of the specification was not germline-specific. Simply, the Examiner's position cannot be reconciled with the state of the art, wherein MP1 is widely accepted by those of skill in the art to be a germline-specific promoter.

Based on the numerous references of record, it is made abundant that the MP1 promoter is known in the art to be a germline-specific promoter, specifically the male germline. In efforts to confuse the issue, the Examiner points out that the MP1 is referred to as "spermatid-specific", and that "the abstracts do not teach testing in heart, brain or spleen [t]hus, it cannot be determined from the abstracts whether the art accepted definition of 'germline-specific' promoters allowed for expression in other tissues" (see Examiner's Answer, at page 14, lines 18-

21). However, the abstracts refer to "**spermatid-specific expression** of protamine 1 in transgenic mice" and "**tissue-specific protamine expression**" (Peschon, 1987); the fact that "mouse protamine are expressed **exclusively in spermatids**" (Peschon, 1989); and the fact the "mouse protamine 1 (Prm-1) gene is transcribed **exclusively in post-meiotic spermatids** (Sambrowicz, 1993) (emphasis added). There can be no question that one of skill in the art would readily recognize the MP1 promoter to be germline-specific.

Appellant further disagrees with the Examiner's improper use of only a portion of the definition of tissue specific in the specification, quoting the example provided, rather than the definition itself. The entire definition states "the term 'tissue specific' refers to the **substantially** exclusive initiation of transcription in the tissue from which a particular promoter, which drives expression of a given gene, is derived (e.g., expressed only in T-cells)" (emphasis added, see specification at page 8, lines 15-18). The MP1 promoter, as an exemplary germline-specific promoter, clearly meets this definition, as recognized by those of skill in the art.

Therefore, the specification as filed clearly enables any germline-specific promoter (see Appeal Brief at page 14-16; and see, for example, specification at page 6, lines 1-12, and page 8, lines 14-19).

The Examiner fails to recognize that both recombinase and a target nucleic acid construct must be present in the ES cells, and thus misunderstands the examples.

The Examiner's discussion of Examples 3 and 5 includes both admissions and contradictory statements that evidence a misunderstanding of the exemplary ES cells and methods performed (see Examiner's Answer, Paper No. 30, at pages 16-17).

Indeed, the same paragraph quoted by the Examiner (see Examiner's Answer, Paper No. 30, at page 16, quoting specification at page 22, lines 10-21) to support the assertion that "the description does not teach ES cells containing both constructs were used to make ProCre/P2Bc mice" (see Examiner's Answer, Paper No 30, at page 16 lines 16-17), in fact teaches that ES cells containing both the Cre recombinase and the target sequence flanked by lox P sites are used

to generate ProCre/P2Bc mice, and this example would be clear to one of skill in the art as follows.

First, founder animals are made containing ProCre constructs. Second, ES cells from these ProCre mice are further transformed with the second target construct (P2Bc) via homologous recombination. Third, the ES cells containing both Cre recombinase and the second target construct are developed through gametogenesis to activate expression of the Cre recombinase, and thus, activate Cre-mediated recombination of the target DNA flanked by lox P sites. It is clear that the ES cells used for further development must contain both the recombinase and the target in order to generate mouse containing the recombined P2Br allele. Therefore, Example 3 teaches ProCre ES cells transfected with a second target construct.

Moreover, the Examiner directly contradicts his position that "the description does not teach ES cells containing both constructs were used to make ProCre/P2Bc mice" (see Examiner's Answer, Paper No 30, at page 16 lines 16-17) by acknowledging, in the next paragraph, that "Example 5 . . . teaches ES cells comprising DNA encoding recombinase transfected with a constructs [sic] flanked by loxP sites" (see Examiner's Answer, Paper No. 30, at page 16-17 bridging sentence); and later noting that "**ES cells having two constructs** had recombination" (emphasis added, see Examiner's Answer, Paper No. 30, at page 17, lines 8-9) Therefore, as acknowledged by the Examiner, Example 5 also teaches ProCre ES cells transfected with a second target construct.

The Examiner fails to recognize the distinction between "homologous recombination" and "recombinase-mediated recombination" in interpreting the examples.

Appellant respectfully submits that the Examiner has clearly misinterpreted the type of recombination taking place in Example 5, as evidenced by the erroneous assertion that Appellant's Appeal Brief argument that ProCre males bred with P2Bc females did not result in recombination is allegedly contradictory to Example 5. In efforts to support this assertion, the Examiner makes the irrelevant observation that "ES cells comprising DNA encoding recombinase transfected with a constructs [sic] flanked by lox P sites has recombination without

becoming an embryo (and therefore without going through spermatogenesis)" (see Examiner's Answer, Paper No. 30, at page 17, lines 1-2).

However, the Examiner clearly fails to recognize that this reference to "recombination" refers to **homologous** recombination in order to effect integration of the second target construct into the genome of the ES cells, and clearly **not Cre-mediated** recombination. Example 5 clearly states "[t]o determine if **homologously recombined** ProCre ES cell clones could be isolated . . . transfections were done . . .", where Southern blot analysis of the ES cell genome confirmed that fragment sizes identified corresponded to the size of fragments "predicted to result from **homologous recombination**" (emphasis added, see specification at page 26, lines 1-13). These same cells are then subjected to transient transfection with immediately active Cre (*i.e.*, no germline-specific promoter) to verify that the homologously recombined clones contained active lox P sites that could be Cre-recombined by the addition of active Cre; here Cre-mediated recombination takes place not due to the germline-specific Cre construct, but merely due to the active Cre construct used to "double check" the functionality of the ProCre/target construct ES cells (see specification at page 26, lines 27-36).

Contrary to the Examiner's assertion, Appellant's prior statements in the Appeal Brief regarding the lack of recombination in female mice due to the male germline-specific promoter are not contradictory to the teachings of Example 5, because no Cre-mediated recombinase takes place in female mice developed from ES cells comprising the two identified constructs.

In summary, the arguments presented in the Appeal Brief and supplemented herein clearly show that the specification "discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim", for each of the methods claimed. Therefore, the enablement requirement of 35 U.S.C. § 112 is satisfied.

2. 35 U.S.C. §112, second paragraph Rejection of Claims 12, 28-32, 34-44 and 46-51

The phrase "passaging the genome derived from said embryonic stem cells through gametogenesis" is definite to one of skill in the art, as evidenced by the Examiner's own statements.

Appellant respectfully submits that the phrase "passaging the genome derived from said embryonic stem cells through gametogenesis" is clear and definite to one of skill in the art, in light of the teachings of the specification. Moreover, the Examiner's discussion of the phrase (see Examiner's Answer, Paper No. 30, at pages 17-18) shows that the Examiner clearly understood the language of the claims in light of the specification as filed.

The Appeal Brief makes it clear that one of skill in the art would recognize that in order to generate recombinase in the ES cells transfected with a recombinase activated by a germline-specific promoter, one would passage the ES cells through gametogenesis, *i.e.*, to develop an embryo from the ES cells through the point at which either spermatogenesis or oogenesis occurs in development (see Appeal Brief, at page 23, lines 19-25). The crux of the invention is the germline-specific activation of the recombinase. The methods of the invention requiring recombinase activation are therefore not fulfilled without passaging the ES cells through the developmental point where germline-specific promoters would activate the recombinase. This is how the crux of the invention is intimately correlated with the passaging step.

Moreover, the Examiner has himself provided an exemplary method of passaging the ES cells through gametogenesis; specifically by implanting ES cells into a uterus to obtain an embryo that undergoes gametogenesis (see Examiner's Answer, Paper No. 30, at page 18, lines 3-5). Thus, the Examiner has clearly understood a method of passaging the ES cells through gametogenesis, as contemplated by the specification.

Appellant is free to choose his own terminology, *i.e.*, the use of "passaging" in a broader sense than just cell culture manipulation as presented by the Examiner (see Examiner's Answer, Paper No. 30, at page 18, lines 3-4), as long as it is clear to one of skill in the art. Thus, the

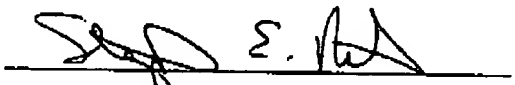
Examiner's own statements show that the phrase is clear and definite in light of the teachings of the specification. Therefore, the phrase is definite and fully supported by the specification as filed.

V. Conclusion

For the reasons discussed in Appellant's Appeal Brief, as further elaborated above, Appellant respectfully submits that the instant claims are in condition for allowance. Accordingly, Appellant respectfully requests that all rejections be withdrawn or reversed, and that the claims be allowed to issue.

Respectfully submitted,

Date: August 5, 2002



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